Imperial College London

Research Governance and Integrity Team

Imperial College Healthcare NHS Trust

VIP study

SARS-CoV2 **V**accination immunogenicity
in **I**mmunosuppressed inflammatory bowel disease **P**atients

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MAIN SPONSOR: Imperial College London
FUNDERS: Pfizer
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IRAS Project ID: **292123**
REC reference: 21/WA/0105

Protocol authorised by:

Name & Role	Date	Signature
Dr Nick Powell	26/04/2020	

Study summary

SARS-CoV2 infection has caused a global health emergency and has killed 1 in a 1000 of the British population. Vaccination holds the key to protecting individuals and limiting viral transmission at a population level. Despite the optimism generated by the phase III SARS-CoV2 vaccination studies, there are important knowledge gaps, particularly regarding some of the most vulnerable members of society. None of the vaccines have been tested in patients taking immunosuppressive drugs. Not only are these patients likely to be at high risk of COVID-19 disease, but the immunosuppressive drugs that they take may compromise the ability of vaccines to stimulate protective immune responses. This important knowledge gap could have grave implications for millions of immunosuppressed patients across the globe, who would remain unprotected from SARS-CoV2 infection even after vaccination.

Anti-TNF agents such as Infliximab are one of the most commonly used immunosuppressive drugs in the world. They are efficacious in several immune-mediated inflammatory diseases (IMIDs) such as inflammatory bowel disease (IBD), but they have an important Achilles heel. They significantly impede the generation of protective immune responses to various commonly used vaccines. This study will specifically determine whether anti-TNF treatment, and other immunosuppressive agents used in IBD, reduce the ability of patients to mount durable, protective humoral and cell-mediated immune responses after SARS-CoV2 vaccination. Vedolizumab, which has a gut-specific mode of action and does not impair immune responses to other vaccines, is being used as the control arm of the study.

IBD patients (n=600) from thirteen UK centres who have undergone vaccination against SARS-CoV2 will be identified in the NIHR IBD Bioresource and recruited according to which therapies they are prescribed: Thiopurines (n=100), Infliximab (n=100), Infliximab + thiopurine (n=100), Vedolizumab (n=100), Ustekinumab (n=100) and Tofacitinib (n=100). Healthy people without IBD(n=200) will be also be recruited. Blood sampling will be performed between days 60 and 85 (+/-7 day window) after the second dose of SARS-CoV2 vaccination and 35-42 days (+/-7 day window) after the third (or booster) dose of SARS-CoV2 vaccination, and tested for anti-SARS-CoV2 antibodies and antigen-specific T-cell responses. The primary endpoint of the study is immunogenicity to routinely administered SARS-CoV2 vaccination at the first visit (between days 60-85) post second dose of vaccination, measured as the geometric mean titre of neutralising anti-SARS-CoV2 antibodies in IBD patients on Infliximab treatment compared to non-IBD participants, stratified by vaccine type, with no evidence of prior infection. Secondary endpoints include immunogenicity to vaccination at the first visit (between days 60- 85) post second dose of vaccination, measured as the geometric mean titres of S1 binding IgG and RBD IgG antibodies, immunogenicity to vaccination at the second visit (35-42 days post third dose), and adaptive immune response to vaccination measured using T cell assays and longitudinal transcriptomics in each study arm.

Study Management Group

Chief Investigator: Dr Nick Powell & Professor Tariq Ahmad

Co-investigators: Prof Ailsa Hart, Dr Peter Irving, Prof Shaji Sebastian, Prof Charlie Lees, Dr Nick Kennedy, Dr James Goodhand, Dr Alex Kent, Dr Kamal Patel, Dr Lucy Hicks, Dr Charles Murray, Dr Klaartje Kok, Dr Shameer Mehta, Dr Francesca Fiorentino, Dr Katrina Pollock, Dr Miles Parkes, Dr James Lee, Dr James Alexander

Statistician: Dr Francesca Fiorentino

Study Management:

The SMG will comprise a chair, a lay person, a representative of the sponsor, a gastroenterologist, chief investigators, trial manager, a senior NHS research nurse and the trial statistician. Specific roles will include:

- Reviewing the Protocol to ensure the study will address the project's specific aims
- Recommending and reviewing proposed protocol changes.
- Monitoring performance, including recruitment, retention, overall study progress, and adherence to study protocol.
- Evaluating patient safety. Determining when patients and local PIs should be notified about positive or abnormal findings.
- Assessing data quality and quality control procedures.
- Evaluating the data analytical plan.
- Evaluating the publication plan, including topics and preparation schedule.
- Reviewing and providing recommendations prior to submission of any manuscript

Study Coordination Centre

For general queries, supply of study documentation, and collection of data, please contact:

Study Manager: Claire Bewshea
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Clinical Queries

Clinical queries should be directed to the study co-ordinator, Dr James Alexander and Dr Nick Powell (CI)

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Research Governance and Integrity at:

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Funder

Pfizer (Grant Application ID #66798527) is funding the study.

This protocol describes the VIP study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

IBD	Inflammatory Bowel Disease
CD	Crohn's Disease
UC	Ulcerative Colitis
IMID	Immune-Mediated Inflammatory Disease
SARS-CoV2	Severe Acute Respiratory Syndrome Coronavirus 2
COVID-19	Coronavirus Disease of 2019
TNF	Tumour Necrosis Factor
LC-MS	Liquid Chromatography – Mass Spectrometry
NMR	Nuclear Magnetic Resonance
PBMC	Peripheral Blood Mononuclear Cell
FCP	Faecal Calprotectin
CRP	C-Reactive Protein
HBV	Hepatitis B Virus
RNA	Ribonucleic Acid
DNA	Deoxyribonucleic Acid
CRF	Clinical Research Facility
eCRF	Electronic Case Report Forms
ICTU	Imperial Clinical Trials Unit
EDC	Electronic Data Capture
SMG	Study Management Group

KEYWORDS
SARS-CoV2, COVID-19, Vaccination, Immunogenicity, Inflammatory bowel disease, Immunosuppression

STUDY SUMMARY

TITLE	SARS-Cov2 **V**accination **I**mmunogenicity in inflammatory bowel disease **P**atients
DESIGN	Prospective observational clinical study
AIMS	To determine the immunogenicity of SARS-CoV2 vaccination in patients with inflammatory bowel disease on immunosuppressive treatments undergoing vaccination as part of routine clinical care.
OUTCOME MEASURES	**Primary:** Immunogenicity to routinely administered SARS-CoV2 vaccination at day 60-85 post second dose of vaccination, measured as the geometric mean titre of Anti-SARS-CoV-2 spike (S) antibodies (Roche Elecsys immunoassay)in IBD patients on immunosuppressive treatment regimens compared to non-IBD control participants. **Secondary:** Immunogenicity to vaccination at the first visit (between days 60- 85) post second dose of vaccination, measured as the geometric mean titres of S1 binding IgG and RBD IgG antibodies in IBD patients on immunosuppressive treatment regimens compared to non-IBD control participants. Immunogenicity to a third dose (or booster dose) of vaccination at the second visit, 35-42 days (+/- 7 days) following the third dose, measured as the geometric mean titres of neutralising anti-SARS-CoV2 antibodies, S1-binding IgG antibodies and RBD IgG antibodies in IBD patients. Proportion of IBD patients on immunosuppressive treatment regimens compared to non-IBD control participants with seroprotection against SARS-CoV2 at the first visit (between days 60- 85) and at the second visit (35-42 days following third dose of vaccine). Adaptive immune response to vaccination measured using T cell assays and longitudinal transcriptomics in each study arm.
POPULATION	Adult IBD patients and healthy participants
ELIGIBILITY	Adult patients with an established diagnosis of CD or UC, using standard definitions of IBD, undergoing vaccination against SARS-CoV2. Healthy participants without inflammatory bowel disease who are not immunosuppressed.

DURATION 12 months

1. INTRODUCTION

1.1. BACKGROUND

The coronavirus disease of 2019 (COVID-19) pandemic is caused by a novel RNA coronavirus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), not previously known to infect humans[1,2]. SARS-CoV2 causes life-threatening pneumonia, acute respiratory distress syndrome and multi-organ failure[1,2], which has been responsible for a global health emergency. Effective treatment and prevention strategies are urgently needed. Vaccination is likely to be a key weapon to protect the health of the world's population from COVID19 and is likely to be especially important in high risk individuals, such as those with pre-existing conditions[3]. Without a vaccine, the World Health Organisation estimates that 80% of the world population will eventually become infected by this deadly virus.

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC) is a typical immune-mediated inflammatory disease (IMID), estimated to affect 620,000 people in the UK, and its incidence continues to increase globally[4,5]. Like many patients with other IMIDs, IBD patients take immunosuppressive drugs, which leaves them vulnerable to infection[6,7]. Indeed, concerns about the health of IMID patients during the COVID-19 pandemic has led to the introduction of radical and unprecedented health policies, including mandatory prolonged physical distancing measures, such as shielding. However, the risks associated with immunosuppression are not limited to increased susceptibility to infection. Immunosuppressive drugs may reduce the effectiveness of some vaccines, which could have major implications for the safety of immunosuppressed patients in the COVID-19 era. However, this phenomenon is not uniform or predictable, and moreover, the immunogenicity of different vaccines may be completely different even in the same patient. In patients with IBD, infliximab monotherapy is linked to impaired induction of protective immunity following hepatitis B (HBV), hepatitis A, pneumococcal or influenza vaccination[8-14]. Importantly, serological protection is especially poor for RNA viruses (such as influenza) in anti-TNF treated IBD patients[11,13-16], and are especially defective in patients concomitantly prescribed immunomodulators[17-19]. A summary of immunogenicity data from vaccine studies in patients taking immunosuppressive therapies is shown in figure 1. On the other hand, vedolizumab, which has a gut specific mechanism of action, does not hinder hepatitis B or influenza vaccination responses, although is associated with impaired antibody responses from gut delivered vaccination, such as cholera toxin[15,20]. There is a lack of data for some of the newer drugs used in IBD, although lessons have been learned in other IMIDs. For instance, in psoriasis, antibody responses to pneumococcal and tetanus vaccines are

preserved, and possibly even enhanced in patients treated with ustekinumab, a monoclonal antibody that blocks the p40 subunit of IL12 and IL23[19]. In rheumatoid arthritis, tofacitinib results in diminished induction of protective immune responses to pneumococcal vaccination, but responses to influenza vaccination are maintained[21]. Accordingly, there is a pressing need to understand whether different immunosuppressive regimens used in IBD impair the development of anti-SARS-CoV2 immunity in this high-risk population.

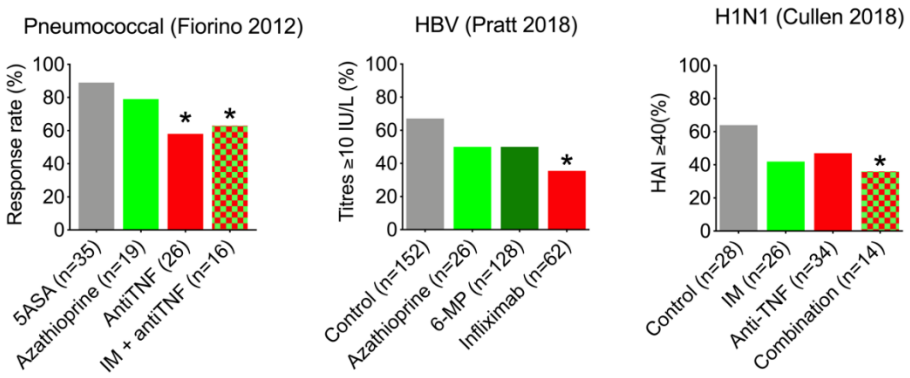

Figure 1: Summary of studies of immunogenicity of vaccines in patients taking immunosuppressive therapies

The value proposition in recognizing which drugs are associated with impaired immunization success, is that alternative vaccination strategies could be employed. For instance, high-dose vaccination overcomes the otherwise reduced efficacy of standard dose influenza immunization in anti-TNF treated IBD patients[15]. In addition, these data could be used to inform preferred drug regimens during the COVID era, particularly if some immunosuppressive treatments are associated with very poor vaccination responses.

Three SARS-CoV2 vaccines have now shown impressive efficacy in reducing infection rates, including 2 RNA vaccines (Pfizer and Moderna)[22] and an adenovirus vector developed by Oxford/Astra Zeneca[23]. This study will test whether IBD patients taking specific immunosuppressive drugs have reduced vaccine immunogenicity after they have been enrolled in the national vaccination program.

1.2. RATIONALE FOR CURRENT STUDY

The purpose of this study is to determine the immunogenicity of routinely administered SARS-CoV2 vaccination in IBD patients stratified by the different types of immunosuppressive drugs that they are prescribed. We will also investigate mechanisms of successful vaccination.

We will test the following hypotheses:

- *Titres of anti-SARS-CoV2 antibodies following vaccination will be reduced in IBD patients prescribed anti-TNF therapy.*

- *The durability of antibodies against SARS-CoV2 following vaccination will be reduced in IBD patients prescribed anti-TNF therapy.*
- *SARS-CoV2 antigen-specific T-cell responses following vaccination will be reduced in IBD patients prescribed anti-TNF therapy*

Research question 1: Do immunosuppressive drugs impact SARS-CoV2 vaccination immunogenicity in IBD patients?
We will determine whether different immunosuppressive regimens are associated with reduced vaccine immunogenicity in IBD patients. Blood will be sampled at 2 time points (days 60-85 after the second dose and 35-42 days post the third dose of vaccine..

Research question 2: Do immunosuppressive drugs impede the durability of anti-SARS-CoV2 antibodies in IBD patients?
Through longitudinal sampling we will determine whether different immunosuppressive regimens are associated with reduced vaccine immunogenicity in IBD patients. Blood will be sampled at 2 time points (days 60-85 after the second dose and 35-42 days post the third dose of vaccine.

Research question 3: Do immunosuppressive drugs impact on SARS-CoV2 reactive T-cell responses in IBD patients?
Given the importance of T-cells in anti-viral immunity and supporting effective humoral responses[24], we will also examine whether IBD patients established on different immunosuppressive regimens exhibit impaired viral-specific T-cell responses.

Benefits
This protocol addresses clinically relevant priority research questions relating to SARS-CoV-2 in a vulnerable patient group. Understanding the impact of therapeutic drugs will help to mitigate risk in these patients.

Risks
This is an observational study and is low risk. The collection of blood samples for research purposes is not anticipated to pose a significant risk to patients.

2. STUDY OBJECTIVES

Primary Objectives:
The primary objective of this study is to assess the immunogenicity of SARS-CoV2 vaccination in patients with IBD, stratified by IBD treatment.

Secondary Objectives:
- To assess the immunogenicity of a third (or booster) dose of SARS-CoV2 vaccination in IBD patients, stratified by IBD treatment.

- To assess the impact of immunosuppressive drugs on post-vaccination SARS-CoV2 reactive T-cell responses in IBD patients.

3. STUDY DESIGN

This is a prospective observational study assessing the immunogenicity of SARS-CoV2 vaccination in IBD patients according to the immunosuppressive medications that they take.

Study subjects

Recruitment will take place from the following settings.

- IBD patients identified in the IBD bioresource.
- Biologic infusion units
- By screening of patient databases (e.g. databases of patients receiving biologics)
- Non-IBD healthy participants these patients will be invited to participate either through word of mouth, adverts/posters or through existing healthy volunteer databases.

Patient identification Centres (PIC)
We will use patient identification centres (PIC) to identify suitable patients from trusts around the research centres. The PIC sites will be only identifying patients and referring them to the research centre.

We will recruit 600 IBD patients stratified according to the immunosuppressive medication they are on. Patients must have been for at least 3 months on the following treatments: thiopurines (n=100), infliximab (anti-TNF) (n=100), combination infliximab/thiopurines (n=100), vedolizumab (n=100), ustekinumab (n=100) and tofacitinib (n=100). We will also recruit 200 healthy people without IBD.

The schedule of events documenting each study visit and the procedures to be performed is illustrated in **Appendix 1**. Following pre-screening (further information in protocol section 4.1), participants will be consented and enrolled in the study. Details including IBD phenotype, patient demographics and disease activity will be collected via the patient questionnaires, which will be completed after study consent is given.

In September 2021, the UK government announced plans for third vaccine doses (or booster doses) for immunosuppressed people. In order to determine the impact of third vaccine doses on immunogenicity, the second study visit will now take place 35-42 days after the third dose is given.

40mL blood draw will be sampled at 2 time points, after 2nd dose of vaccination (days 60- 85*), and 35-42 days* post third dose of vaccine, to assess serology and T-cell responses.

A subset of patients with poor vaccine responses (n=20) and another subset with robust vaccine responses (n=20) will be invited to provide a further blood sample for

more extensive T-cell work, to further probe mechanisms of failed vaccination. This can be performed at the second visit.

We anticipate that all patients will be recruited into the study within six months of commencement. The study will run for 12 months, from the recruitment of the first patient.

*time points will include an allowance of 1 week either side.

Data collection and management

Patients recruited at London sites will attend the Imperial Peart Rose, Hammersmith Hospital for their study visits. Patients recruited at non-London sites, including Cambridge, Edinburgh, St Marks, Barts Health and Exeter, will attend their local site for sampling. Source data, including original documents related to the study, and adequate source documentation will be maintained to allow reliable verification and validation of the study data.

Patient Questionnaires will be used to collect study data electronically via the Redcap system. Participants will be prompted to complete a secure on-line questionnaire after consenting to the study. At the time of consent participants will choose whether they receive electronic links to the questionnaires via an email or SMS message. Access to the questionnaire will require the participant to enter their name and date of birth. In order to capture information relating to booster doses, a questionnaire will be administered around the point of the second blood sample.

This REDCap database is held on a secure server within the data centre at the Royal Devon and Exeter NHS Foundation trust which been subjected to external penetration testing. This application has been approved by the information governance team and a DPIA is in place.
Authorised members of local research teams will have access, via two factor authentication and high-grade-security acceptable passwords provided through Active Directory and a permissions database within the application. All access to and modifications of the database are logged, so user errors can be easily tracked if needed.
The database will automatically be backed up by the IT department on a daily basis. No master electronic files will be stored on local drives i.e. the C drive of a PC or laptop as these files are not backed up.

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All trial documentation will be archived for a minimum of 10 years following the end of the trial.

All patients will be offered up to £40 travel expenses to cover both blood collection visits. At some sites this will be reimbursed through the locally available methods at the second visit.

Personal Data

We will process personal data including name, date of birth, gender, ethnic origin, postcode, NHS, CHI number, email and/or mobile telephone numbers under Regulation 3(3) of COPI. The name, date of birth, email and mobile phone numbers are required so that patients can receive electronic links to, and access, the e-consent form and patient questionnaires. The postcode will be used to analyse immune responses to vaccination accounting for regional and deprivation index covariates. Access to these data will only be available to individuals, nominated by the data controller, who have received appropriate information governance and asset owner training. These data will not be available to members of the central research team who will be granted access to de-identified data only. A participant's rights to access, change or move information will be limited, to ensure the data is reliable and accurate. If a participant chooses to leave the study we will keep information about them that has already been collected. It is anticipated that a small number of participants might decide not to participate having been emailed the e-consent form. Personal data relating to these participants will be removed within 7 days.

What will happen to samples at the end of the study?

Samples will be transferred into the established fully regulated Imperial Hepatology & Gastroenterology Biobank (current REC ref. 20/SC/0389) which comes under Imperial College Healthcare NHS Trust HTA Licence ref. 12275.

Laboratory procedures

Immunogenicity

Serological responses will be recorded at 2 time points post vaccination (days 60- 85 after the second dose is administered and 35-42 days after the third dose is administered). Specifically, we will perform Roche Elecsys Anti-SARS-CoV-2 spike (S) immunoassay, SARS-CoV-2–specific WT serum neutralization assay, SARS-CoV-2-spike (S) protein–specific IgG direct Luminex immunoassay and SARS-CoV-2 RBD–specific IgG direct Luminex immunoassay. Serology tests will be performed in the laboratories of Professor Danny Altmann and Professor Rosemary Boyton (Imperial College London) and at the Royal Devon and Exeter Hospital NHS Trust, Blood Science Academic department. The 50% and 90% neutralization titres will be reported as the interpolated reciprocal of the dilutions achieving 50%/90% reductions. Values below the lower limit of quantitation will be defined as 0.5 times the lower limit of quantification.

T-cell assays

T-cell responses

Antigen-specific T-cell responses will be defined at (day 60-85 post second dose and 35-42 days post third dose). PBMC ($5x10^5$) will be plated in an IFNγ enzyme-linked

immunosorbent spot (ELISpot) and cultured for 20 hours with specific antigen stimulation (15-mer peptides (1μg/mL per peptide) from S1-protein, or without peptides (negative control). An additional positive control (agonistic anti-CD3 antibodies) will be plated for each sample.

Extended lymphocyte studies in responders and non-responders
A subset of IBD patients with either poor vaccine responses (n=20) or robust vaccine responses (n=20) will be recalled for more detailed T-cell and B-cell assays, which will include a further blood draw of 40mL.

Transcriptomics
Transcriptomic analysis will be performed to further elucidate the mechanisms of immune responses to vaccination.

Samples collected in the VIP study may be sent to and analysed at key collaborator laboratories.

Returning results to patients
Knowledge of test results may lead patients to change their physical distancing behaviour even though it is currently unknown whether, or for how long, a test confers immunity. However, the CLARITY IBD patient survey has clearly demonstrated that even when patients are made aware of these limitations, they still wish to have results returned to them. Therefore, we will notify patients via email when their Elecsys® Anti-SARS-CoV-2 'N' and 'S' antibody test results are available, and they will retrieve this following authentication with REDCap. Research teams at study sites will also have access to results through REDCap. When returning results, we will emphasise the uncertainty regarding what a positive test means for an individual in terms of immunity. We will encourage the patients to continue to follow appropriate physical distancing measures as advised by the UK government

3.1. STUDY OUTCOME MEASURES

Primary endpoint:

The geometric mean titre of Anti-SARS-CoV-2 spike (S) antibodies at days 60- 85 (post second vaccine dose) in IBD patients prescribed Infliximab in comparison with non-IBD participants (control arm).

Secondary endpoints:

The geometric mean titre of neutralising anti-SARS-CoV2 antibodies at 35-42 days post third dose of vaccine in IBD patients prescribed Infliximab therapy in comparison with non-IBD participants (control arm).

The geometric mean titre of neutralising anti-SARS-CoV2 antibodies at days 60- 85 (post second vaccine dose) and at 35-42 days post third dose of vaccine in IBD patients prescribed other IBD medications in comparison with non-IBD participants (control group).

The geometric mean titre of S1-binding IgG antibodies and RBD IgG antibodies at day 60-85 (post second vaccine dose) and at 35-42 days post third dose of vaccine in IBD patients on anti-TNF therapy and other IBD medications compared to non-IBD participants (control arm).

Proportion of IBD patients on immunosuppressive treatment regimens compared to non-IBD participants with seroprotection against SARS-CoV2 at days 60- 85 and at 35-42 days post third dose of vaccine

T cell and transcriptomic responses in IBD patients stratified by medication.

4. PARTICIPANT ENTRY

4.1. PRE-REGISTRATION EVALUATIONS

Patients will be contacted prior to entry into the study by a member of their clinical team for pre-enrolment screening and to check whether they would be interested in participating in the study. Information will be provided on the study and a patient information sheet will be sent out/emailed by a member of their clinical team. Screening will include an assessment of IBD disease activity. Inclusion and exclusion criteria will be assessed and applied as detailed in protocol sections 4.2 and 4.3.

Consent

Invitations will be sent out electronically, either through an email or a text message. For patients who do not have access to electronic devices the information will be sent via Royal Mail. Patients may also be provided with this information at the time of the IBD treatment infusions but they must be given sufficient time to decide whether they would like to take part and given the opportunity to ask questions.

Patients who lack capacity to consent will not be recruited.

Patients will be informed of the nature and purpose of the study, its requirements (including a need to hold personal data) and possible hazards, and their rights to withdraw at any time from the study without prejudice and without jeopardy to any future medical care at the study site at the time of consent.

4.2. INCLUSION CRITERIA

- Adults (aged ≥18 years)
- Established diagnosis of CD or UC using standard definitions of IBD or healthy people without IBD.
- Established on current immunosuppressive regimen (as listed in ‘study subjects’ section) for at least 12 weeks. This criteria does not apply to healthy participants without IBD.
- Receiving vaccination against SARS-CoV2
- Able to give informed consent.

4.3. EXCLUSION CRITERIA

- Unable to give informed consent
- Patients <18 years of age
- Recipients of 'accelerated dosing' of vaccination (I.e. second dose of SARS-CoV-2 vaccination given within 42 days of first dose).
- Patients on any other immune suppressants to those listed in study subjects section (other than oral steroids).
- Excluded medication include:
- adalimumab
- golimumab
- certolizumab
- mesazaline
- mycophenolate
- tacrolimus
- thalidomide
- ciclosporin.
- cyclophosphamide.
- hydroxychloroquine.
- leflunomide.
- methotrexate.
- mycophenolate.
- sulfasalazine.

4.4. WITHDRAWAL CRITERIA

Participants may choose to withdraw from the study at any time but their pseudonymised biological samples will be retained. The reason for withdrawal must be documented in the electronic CRF and a withdrawal log should be completed.

5. ADVERSE EVENTS

5.1. DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

This is an observational study in which the only interventions are two blood draws. Only adverse events directly related to the blood draws (e.g. a vasovagal episode) will be reported. Other adverse events which take place during the course of the study but are not directly related to the blood draws will not be reported. It is not anticipated that there will be any serious adverse events in this study.

5.2. REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded- it should be specified if only some non-serious AEs will be recorded, any reporting should be consistent with the purpose of the trial end points.

5.3.2 Serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours.

All SAEs should be reported to the Wales Research Ethics Committee (REC) where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all related and unexpected SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
RGIT@imperial.ac.uk
CI email (and contact details below)
Fax: xxx, attention xxx
Please send SAE forms to: xxx
Tel: xxx (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

There will be no follow up beyond the second study visit at 35-42 days post third dose of vaccine . The investigations performed in this study are not directly relevant

to the clinical care of the individual participant and it is not anticipated that any relevant incidental findings will be identified.

The study will end after all 650 participants have completed the second study visit at week 26.

7. STATISTICS AND DATA ANALYSIS

Sample size calculation

To inform power calculations we have modelled vaccination responses in IBD patients based on data from the CLARITY-IBD study investigating serological responses to infection and vaccination against SARS-CoV-2 in IBD patients treated with infliximab or vedolizumab[25]. Vedolizumab, an anti-integrin therapy, has a gut specific mechanism of action, which does not impact on systemic immunity. We therefore make the assumption that immune responses of non-immunosuppressed non-IBD participants in VIP will be similar to those of participants in the CLARITY-IBD study who were treated with Vedolizumab.

In the CLARITY-IBD study the mean (not stratified by vaccine type) of the log Anti-S is 5.225 (SD=1.697) in participants on infliximab and 7.084 (SD=1.704) on participants on Vedolizumab. We assume a similar difference in serological response. Based on these assumptions we will need 21 participants in the Infliximab arm and 21 participants in the non-IBD arm to detect a similar difference of 1.859 between the infliximab Group and the non-IBD group, with 90% power and 0.05 significance and 5% loss of participants due to evidence of prior SARS-CoV2 infection at baseline.

If we assume that other drugs will only suppress antibody responses by 50% of what Infliximab does, and a similar estimate for the SD, we will need 80 participants in one of the other drug groups and 80 participants in the non-IBD group to detect a difference of 0.93, with 90% power and 0.05 significance and 5% loss of participants due to positive SARS-CoV2 serology at baseline.

Therefore, we will recruit 100 patients in each study arm, and 200 participants in the non-IBD arm.

Data analysis plan

The data analysis will be led by the senior statistician (Dr Francesca Fiorentino) and the study statistician at ICTU and it will be informed by a Statistical Analysis Plan (SAP) which will be written and signed off by the research team and the TSC ahead of seeing the data and commencing the analysis. For immunogenicity end points, all analyses will be based on comparisons of the anti-TNF-treated group to non-IBD control subjects. Geometric mean titres/concentrations (GMC/GMC) of SARS-CoV2 neutralizing antibodies (S1 binding IgG levels, RBD-binding IgG levels) will be calculated with 2-sided 95% CI according to each IBD treatment strata at visit one

and visit two. Geometric means will be calculated as the mean of the assays after making logarithm transformation and exponentiating the mean to express results on the original scale. 2-sided 95% CI (with reference to the t-distribution) and then exponentiating the confidence limits.

Titres below the level of detection will be given a nominal value of 0.5 of the lower limit of detection of the assay. Missing serology data will not be imputed. To test the immunogenicity of a third vaccine dose in the different treatment groups, the changes in the GMT of SARS-CoV2 neutralizing antibodies, S1 binding IgG levels and RBD-binding IgG levels will be calculated (with 95% CI) and compared with the results 35-42 days following the third dose.

Other exploratory endpoints analysis will include multivariate and univariate modelling and statistical tests, which will be outlined in the SAP.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1. ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the Wales Research Ethics Committee (REC) and Health Research Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2. CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3. CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4. INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study

8.5. SPONSOR

Imperial College London/ will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6. FUNDING

Applications for funding will be made to Pfizer, the NIHR/UKRI and other research councils. Industry partnerships will be also be sought to provide funding. Pump prime funding from University grants are also being requested.

8.7. AUDITS

The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the Study Manager, Claire Bewshea.

10. PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the Study Management Group, to include the Chief Investigators and Co-Investigators. Members of the Study Management Group will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Study Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Study Management Group and the Study Coordination Centre.

Patient & Public Engagement

Our research question is considered important by patients with IBD. We have conducted an extensive national patient and public involvement exercise of 396 IBD patients from 66 IBD centres across our research network, including 60 IBD patients from Imperial College NHS Trust. This is an important issue given potential concerns about vaccines by some sectors of society, which could theoretically compromise recruitment. In this exercise >90% of our patients believed that understanding whether IBD drugs would affect success of any potential SARS-CoV-2 vaccination was either "very important" (67.8%) or "important" (22.3%) (Figure 2).

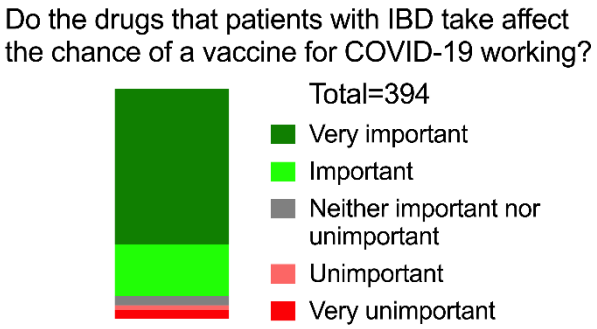

Figure 2: Bar plot showing that >90% of patients believe that understanding whether IBD drugs would affect success of any potential SARS-CoV-2 vaccination was either "very important" (67.8%) or "important" (22.3%)

Our patient groups have reviewed the study protocol, supported the writing of the patient information sheet, advised on the recruitment process and the development of our electronic patient consent and questionnaire.

11. REFERENCES

1. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet (London, England)* 2020; **395**(10223): 507-13.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet (London, England)* 2020; **395**(10223): 497-506.
3. El-Gabalawy H, Guenther LC, Bernstein CN. Epidemiology of immune-mediated inflammatory diseases: incidence, prevalence, natural history, and comorbidities. *J Rheumatol Suppl* 2010; **85**: 2-10.
4. Jones GR, Lyons M, Plevris N, et al. IBD prevalence in Lothian, Scotland, derived by capture-recapture methodology. *Gut* 2019; **68**(11): 1953-60.
5. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018; **390**(10114): 2769-78.
6. Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. *Gastroenterology* 2018; **155**(2): 337-46.e10.
7. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *The American journal of gastroenterology* 2012; **107**(9): 1409-22.
8. Pratt PK, Jr., David N, Weber HC, et al. Antibody Response to Hepatitis B Virus Vaccine is Impaired in Patients With Inflammatory Bowel Disease on Infliximab Therapy. *Inflammatory bowel diseases* 2018; **24**(2): 380-6.

9. Fiorino G, Peyrin-Biroulet L, Naccarato P, et al. Effects of immunosuppression on immune response to pneumococcal vaccine in inflammatory bowel disease: a prospective study. *Inflammatory bowel diseases* 2012; **18**(6): 1042-7.
10. Melmed GY, Agarwal N, Frenck RW, et al. Immunosuppression impairs response to pneumococcal polysaccharide vaccination in patients with inflammatory bowel disease. *The American journal of gastroenterology* 2010; **105**(1): 148-54.
11. Mamula P, Markowitz JE, Piccoli DA, Klimov A, Cohen L, Baldassano RN. Immune response to influenza vaccine in pediatric patients with inflammatory bowel disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2007; **5**(7): 851-6.
12. Park SH, Yang SK, Park SK, et al. Efficacy of hepatitis A vaccination and factors impacting on seroconversion in patients with inflammatory bowel disease. *Inflammatory bowel diseases* 2014; **20**(1): 69-74.
13. Hagihara Y, Ohfuji S, Watanabe K, et al. Infliximab and/or immunomodulators inhibit immune responses to trivalent influenza vaccination in adults with inflammatory bowel disease. *Journal of Crohn's & colitis* 2014; **8**(3): 223-33.
14. Lu Y, Jacobson DL, Ashworth LA, et al. Immune response to influenza vaccine in children with inflammatory bowel disease. *The American journal of gastroenterology* 2009; **104**(2): 444-53.
15. Caldera F, Hillman L, Saha S, et al. Immunogenicity of High Dose Influenza Vaccine for Patients with Inflammatory Bowel Disease on Anti-TNF Monotherapy: A Randomized Clinical Trial. *Inflammatory bowel diseases* 2020; **26**(4): 593-602.
16. deBruyn J, Fonseca K, Ghosh S, et al. Immunogenicity of Influenza Vaccine for Patients with Inflammatory Bowel Disease on Maintenance Infliximab Therapy: A Randomized Trial. *Inflammatory bowel diseases* 2016; **22**(3): 638-47.
17. Cullen G, Bader C, Korzenik JR, Sands BE. Serological response to the 2009 H1N1 influenza vaccination in patients with inflammatory bowel disease. *Gut* 2012; **61**(3): 385-91.
18. Gelinck LB, van der Bijl AE, Visser LG, et al. Synergistic immunosuppressive effect of anti-TNF combined with methotrexate on antibody responses to the 23 valent pneumococcal polysaccharide vaccine. *Vaccine* 2008; **26**(27-28): 3528-33.
19. Andrisani G, Frasca D, Romero M, et al. Immune response to influenza A/H1N1 vaccine in inflammatory bowel disease patients treated with anti TNF-alpha agents: effects of combined therapy with immunosuppressants. *Journal of Crohn's & colitis* 2013; **7**(4): 301-7.
20. Wyant T, Leach T, Sankoh S, et al. Vedolizumab affects antibody responses to immunisation selectively in the gastrointestinal tract: randomised controlled trial results. *Gut* 2015; **64**(1): 77-83.
21. Winthrop KL, Silverfield J, Racewicz A, et al. The effect of tofacitinib on pneumococcal and influenza vaccine responses in rheumatoid arthritis. *Annals of the rheumatic diseases* 2016; **75**(4): 687-95.
22. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *The New England journal of medicine* 2020.
23. Voysey M, Clemens SAC, Madhi SA, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2020.

24. Vardhana SA, Wolchok JD. The many faces of the anti-COVID immune response. *J Exp Med* 2020; **217**(6).

Appendix 1. Summary of investigations and assessments*

	0	1 (day 85** post vaccination)	2 (35-42 days** post third dose of vaccination)
Pre-screening	X		
Informed consent	X		
Patient questionnaire	X		x
Blood sample (40-50mL)		X	X

* A subset of patients with poor vaccine responses (n=20) and another subset with robust vaccine responses (n=20) will be invited to provide a further blood draw for more extensive T-cell work, to further probe mechanisms of failed vaccination. This can be performed at the second study visit.

**time points include an allowance of 1 week either side.